

## U S APPLICATION NO. (If known, see 37 C.F.R. 1.5)

(10/97)

U.S. APPLICATION NO. <b>09/117810</b>		INTERNATIONAL APPLICATION NO. PCT/DE97/00245		ATTORNEY'S DOCKET NUMBER 012627-007	
17. <input checked="" type="checkbox"/> The following fees are submitted:				<b>CALCULATIONS</b>	PTO USE ONLY
<b>Basic National Fee (37 CFR 1.492(a)(1)-(5)):</b>  Search Report has been prepared by the EPO or JPO ..... \$930  International preliminary examination fee paid to USPTO (37 CFR 1.482) ..... \$720.00 No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) ..... \$790.00  Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO ..... \$1070.00  International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... \$98.00  <div style="text-align: right;"><b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b></div>				\$ 930	
Surcharge of \$130.00 for furnishing the oath or declaration later than months from the earliest claimed priority date (37 CFR 1.492(e)). <input type="checkbox"/> 20 <input type="checkbox"/> 30				\$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	4 -20 =	0	X\$22.00	\$	
Independent Claims	-3 =		X\$82.00	\$	
Multiple dependent claim(s) (if applicable)			+ \$270.00	\$	
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$ 930	
Reduction for 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				\$	
<b>SUBTOTAL =</b>				\$ 465	
Processing fee of \$130.00 for furnishing the English translation later than months from the earliest claimed priority date (37 CFR 1.492(f)). <input type="checkbox"/> 20 <input type="checkbox"/> 30				\$	
<b>TOTAL NATIONAL FEE =</b>				\$ 465	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$	
<b>TOTAL FEES ENCLOSED =</b>				\$ 465	
				Amount to be: refunded	\$
				charged	\$
a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>465.00</u> to cover the above fees is enclosed.  b. <input type="checkbox"/> Please charge my Deposit Account No. <u>02-4800</u> in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.  c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. <u>02-4800</u> . A duplicate copy of this sheet is enclosed.					
<b>NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.</b>					
SEND ALL CORRESPONDENCE TO:  <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;">             Teresa Stanek Rea              BURNS, DOANE, SWECKER &amp; MATHIS, L.L.P.              P.O. Box 1404              Alexandria, Virginia 22313-1404           </div> <div style="width: 45%; text-align: right;">               SIGNATURE              Teresa Stanek Rea              NAME              30,427              REGISTRATION NUMBER           </div> </div>					

Applicant or Patentee: Gunther SCHUTZ et al  
Application or Patent No.: 09/117,810  
Filed or Issued: \_\_\_\_\_  
For: SPERMATOGENESIS CONTROL

**VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY  
STATUS (37 C.F.R. §§ 1.9(f) AND 1.27(d)) - NONPROFIT ORGANIZATION**

I hereby declare that I am an official empowered to act on behalf of the nonprofit organization identified below:

NAME OF ORGANIZATION DEUTSCHES KREBSFORSCHUNGSZENTRUM  
STIFTUNG DES OFFENTLICHEN RECHTS  
ADDRESS OF ORGANIZATION Im Neuenheimer Feld 280, D-69120 Heidelberg, Germany

**TYPE OF ORGANIZATION**

- ☐ University or other institution of higher education  
☐ Tax exempt under Internal Revenue Service Code (26 U.S.C. §§ 501(a) and 501(c)(3))  
☐ Nonprofit scientific or educational under statute of state of The United States of America  
(Name of state \_\_\_\_\_)  
(Citation of statute \_\_\_\_\_)  
☐ Would qualify as tax exempt under Internal Revenue Service Code (26 U.S.C. §§ 501(a) and 501(c)(3)) if located in The United States of America  
☐ Would qualify as nonprofit scientific or educational under statute of The United States of America if located in The United States of America  
(Name of state \_\_\_\_\_)  
(Citation of statute \_\_\_\_\_)

I hereby declare that the nonprofit organization identified above qualifies as a nonprofit organization as defined in 37 C.F.R. § 1.9(e) for purposes of paying reduced fees under Sections 41(a) and 41(b) of Title 35, United States Code, with regard to the invention entitled by inventor(s) Gunther SCHUTZ; Julie BLENDY; Klaus KASTNER; Gerhard WEINBAUER; Eberhard NIESCHLAG described in

- ☐ the specification filed herewith  
☒ Application No. 09/117,810, filed \_\_\_\_\_  
☐ Patent No. \_\_\_\_\_, issued \_\_\_\_\_

I hereby declare that rights under contract or law have been conveyed to and remain with the nonprofit organization with regard to the above-identified invention.

If the rights held by the above-identified nonprofit organization are not exclusive, each individual, concern, or organization having rights to the invention is listed below,\* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an individual inventor under 37 C.F.R. § 1.9(c), or by any concern that would not qualify as either a small business concern under 37 C.F.R. § 1.9(d) or a nonprofit organization under 37 C.F.R. § 1.9(e).

**\*NOTE:** Separate verified statements are required from each named person, concern, or organization having rights to the invention averring to their status as small entities. (37 C.F.R. § 1.27.)

FULL NAME \_\_\_\_\_

ADDRESS \_\_\_\_\_  
[ ] individual [ ] small business concern [ ] nonprofit organization

FULL NAME \_\_\_\_\_

ADDRESS \_\_\_\_\_  
[ ] individual [ ] small business concern [ ] nonprofit organization

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earlier of the issue fee and any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 C.F.R. § 1.28(b).)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING	<u>Prof.Dr.med.Dr.h.c.mult.H.zur Hausen</u>	<u>Dr.med.col. J. Puchta</u>
TITLE IN ORGANIZATION	<u>Chairman a. Scient.Member of the Board</u>	<u>Adm.Member of the Board</u>
ADDRESS OF PERSON SIGNING	<u>Eichenstraße 1</u>	<u>Eichenweg 1</u>
	<u>69483 Wald-Michelbach</u>	<u>69198 Schriesheim</u>

SIGNATURE  DATE September 28, 1998

09/117810

201 Rec'd PCT/PTO 10 AUG 1998

Attorney's Docket No. 012627-00

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of )  
Günther Schütz et al ) Group Art Unit: Unassigned  
Application No.: Unassigned ) Examiner: Unassigned  
(Corresponds to PCT/DE97/00245) )  
International Filing )  
Date: 10 February 1997 )  
For: SPERMATOGENESIS CONTROL )

PRELIMINARY AMENDMENT

BOX PCT

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Prior to examination on the merits, please amend the  
above-captioned application as follows:

IN THE CLAIMS:

Kindly amend the claims as follows:

Claim 3, line 2, delete "or 2".

Application Serial No. PCT/DE96/01195  
Attorney's Docket No. 012627-005

REMARKS

Entry of the foregoing amendment is respectfully requested.

The claims have been amended to eliminate multiple dependency and to place them in better condition for U.S. patent practice.

Should the Examiner have any questions concerning the subject application, a telephone call to the undersigned would be appreciated.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: 

Teresa Stanek Rea  
Registration No. 30,427

Post Office Box 1404  
Alexandria, Virginia 22313-1404  
(703) 836-6620

Date: August 10, 1998

Spermatogenesis Control

The present invention relates to a pharmaceutical composition for spermatogenesis control and a process for investigating the spermatogenesis as well as a kit usable therefor.

The development of spermia is referred to as spermatogenesis. It is desired to interfere in spermatogenesis if the latter is unbalanced and does not yield functioning spermia. On the other hand, interference in spermatogenesis could also be made use of to carry out a fertility control in male persons.

Therefore, it is the object of the present invention to provide a product by which spermatogenesis can be controlled.

According to the present invention this is achieved by the subject matters defined in the claims.

Therefore, the subject matter of the present invention relates to a pharmaceutical composition adapted to control spermatogenesis. Such a composition comprises:

- (a) for positive control  
one or more substances of  
CREM (cAMP responsive element modulator), a CREM-phosphorylating compound and a CREM expression inducing compound, and/or
- (b) for negative control  
one or more substances of  
a CREM-inhibiting compound, a CREM phosphorylation inhibiting compound, and a CREM expression inhibiting compound.

The present invention is based on the applicant's finding that CREM (cAMP responsive element modulator) is a decisive regulator of spermatogenesis. The applicant has found that CREM is a transcription factor which controls the expression of proteins involved in spermatogenesis. These proteins are referred to as CREM-dependent proteins in the present application. Examples thereof are proacrosin, protamine, Tp-1 (transition protein-1), MCS (mitochondrial capsule seleno protein) and RT7 (mill germ cell specific protein). If there is CREM deficiency, i.e. if CREM is not expressed or expressed only to a reduced extent and not expressed in phosphorylated form, respectively, so that the above proteins are not expressed either or expressed only to a reduced extent, there will be unbalanced spermatogenesis which results in non-functioning spermia.

In a pharmaceutical composition of the present invention, the expression "a CREM-phosphorylated compound" refers to any compounds adapted to phosphorylate CREM, particularly kinases. In addition, the expression "a CREM expression inducing compound" relates to any compounds which can directly or indirectly induce the expression of CREM. Moreover, the expression "a CREM-inhibiting compound" covers any compounds adapted to inhibit CREM, particularly antibodies directed against CREM. Besides, the expression "a CREM phosphorylation inhibiting compound" denotes any compounds adapted to inhibit the phosphorylation of CREM. Such compounds are particularly kinase-inhibitors, such as H7, H8, H89, HA 1004 and Walsh inhibitor. Furthermore, the expression "a CREM expression inhibiting compound" comprises any compounds which can directly or indirectly inhibit the expression of CREM.

The person skilled in the art knows how to determine which substances mentioned for a pharmaceutical composition of the present invention and which amounts thereof are the best for the spermatogenesis control in an individual proband. For example, the following offers itself to the person skilled in the art: preparation of a transgenic mouse which

which expresses an inducible CREB (cyclic AMP responsive element binding protein) mutant, in round spermatids of the testis. This mutant dimerizes with CREM, the mutant being dominant-negative over CREM, i.e. CREM is inhibited by dimerization with dominant-negative CREB. Therefore, the transgenic mouse enables the determination of substances and the amounts thereof, which influence CREM and thus spermatogenesis.

The introduction of a vector containing a promoter enabling the gene expression in round spermatids, such as the protamine promoter (cf. Zambrowicz, B.P. et al., Proc. Natl. Acad. Sci., U.S.A. 90, (1990), 5071-5075) into inseminated oocytes of a mouse, offers itself for the preparation of the transgenic mouse. This promoter controls a DNA which codes for a fusion protein from the mutated CREB and a modified ligand binding domain of the human progesterone receptor (cf. Wang, Y. et al., Proc. Natl. Acad. Sci., U.S.A. 91, (1994), 8180-8184). The mutated CREB does not have serine but alanine at position 133 and thus cannot be phosphorylated, which signifies the loss of its transcription activity. Amino acids 892-933 are lacking in the modified ligand binding domain of the human progesterone receptor, so that this ligand binding domain can no longer be bound by progesterone but only by the ligand RU 486. The latter serves for activating the mutated CREB in the fusion protein.

A process is also provided according to the invention, which is suited to investigate spermatogenesis and control it, respectively. Such a process comprises the determination of CREM and/or CREM-dependent proteins, e.g. proacrosin, protamine, Tp-1, MCS and RT7.

It is possible to use common methods for determining CREM and/or CREM-dependent proteins. It is favorable to determine by means of PCR methods whether the DNA sequences coding for CREM and/or CREM-dependent proteins include mutations. In addition, the possibility presents itself to puncture the

testis to investigate preferably spermatids and more preferably round spermatids of testes and determine the expression of CREM and/or CREM-dependent proteins. For this purpose, CREM and/or CREM-dependent proteins can be determined in a Western blot analysis in which antibodies are used against the individual proteins. The mRNA of CREM and/or CREM-dependent proteins can also be determined in a Northern blot analysis in which DNAs of the individual proteins are used as samples.

A kit is also provided according to the invention, which is suited to determine CREM and/or CREM-dependent proteins. Such a kit comprises:

One or more of (a) to (c)

- (a) primers for amplifying DNA coding for CREM and/or CREM-dependent proteins,
- (b) antibodies against CREM and/or CREM-dependent proteins, e.g. proacrosin, protamine, Tp-1, MCS and RT7,
- (c) DNA samples for mRNA of CREM and/or CREM-dependent proteins, e.g. proacrosin, protamine, Tp-1, MCS and RT7, as well as
- (d) standards and detection reagents for one or more of (a) to (c), and
- (e) carriers as well as conventional vehicles.

By means of the present invention it is possible to control spermatogenesis, i.e. positively control an unbalanced spermatogenesis, so as to produce functioning spermia and to negatively control normal spermatogenesis thereby inhibiting the formation of spermia. The control of spermatogenesis is reversible, so that the negative control is particularly suitable to control the fertility of a male animal, particularly a male person. By means of the present

invention it is also possible to monitor spermatogenesis, which will be of special importance if controlling interference has been made.

Amended **Claims**

1. A process for investigating spermatogenesis and monitoring it, respectively, wherein CREM and/or CREM-dependent proteins are determined.
2. The process according to claim 1, characterized in that the CREM-dependent proteins are proacrosin, protamine, Tp-1, MCS and/or RT7.
3. A kit for carrying out the process according to claim 1 or 2, comprising one or more of (a) to (c)
  - (a) primers for amplifying DNA coding for CREM and/or CREM-dependent proteins,
  - (b) antibodies against CREM and/or CREM-dependent proteins,
  - (c) DNA samples for mRNA of CREM and/or CREM-dependent proteins, as well as
  - (d) standards and detection reagents for one or more of (a) to (c), and
  - (e) carriers as well as conventional vehicles.
4. A kit according to claim 5, characterized in that the CREM-dependent proteins are proacrosin, protamine, Tp-1, MCS and/or RT7.

### Abstract of the Disclosure

The present invention relates to a pharmaceutical composition, comprising

- (a) for positive control  
one or more substances of  
CREM, a CREM-phosphorylating compound and a CREM  
expression inducing compound, and/or
- (b) for negative control  
one or more substances of  
a CREM-inhibiting compound, a CREM phosphorylation  
inhibiting compound, and a CREM expression inhibiting  
compound.

In addition, the invention concerns a process for investigating spermatogenesis as well as a kit usable for therefor.

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name;

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

SPERMATOGENESIS CONTROL

the specification of which (check only one item below):

☐ is attached hereto.

☐ was filed as United States application

Number \_\_\_\_\_

on \_\_\_\_\_

and was amended

on \_\_\_\_\_ (if applicable).

☒ was filed as PCT international application

Number PCT/DE97/00245

on 10 February 1997

and was amended under PCT Article 19

on \_\_\_\_\_ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(e) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

**PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. §119:**

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. §119
DE	196 04 773.0	09 February 1996	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No
			<input type="checkbox"/> Yes <input type="checkbox"/> No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

\_\_\_\_\_  
(Application Number)

\_\_\_\_\_  
(Filing Date)

\_\_\_\_\_  
(Application Number)

\_\_\_\_\_  
(Filing Date)

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONTINUED)  
(Includes Reference to Provisional and PCT International Applications)

ATTORNEY'S DOCKET NO.  
012627-007

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to the patentability as defined in Title 37, Code of Federal Regulations §1.56, which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. 120:

U.S. APPLICATIONS		STATUS (check one)		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED
PCT APPLICATIONS DESIGNATING THE U.S.				
PCT APPLICATION NO.	PCT FILING DATE	U.S. APPLICATION NUMBERS ASSIGNED (if any)		

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

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Peter H. Smolka 15,913  
Robert S. Swecker 19,885  
Platon N. Mandros 22,124  
Benton S. Duffett, Jr. 22,030  
Norman H. Stepno 22,716  
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and:

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Address all telephone calls to: Teresa Stanek Rea at (703) 836-6620.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONTINUED)  
(Includes Reference to Provisional and PCT International Applications)

ATTORNEY'S DOCKET NO.

012627-007

FULL NAME OF SOLE OR FIRST INVENTOR

SIGNATURE

DATE

Günther SCHÜTZ

27/11/98

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Eberhard NIESCHLAG

3/12/99

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SIGNATURE

DATE

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CITIZENSHIP

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FULL NAME OF SEVENTH JOINT INVENTOR, IF ANY

SIGNATURE

DATE

RESIDENCE

CITIZENSHIP

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FULL NAME OF EIGHTH JOINT INVENTOR, IF ANY

SIGNATURE

DATE

RESIDENCE

CITIZENSHIP

POST OFFICE ADDRESS

FULL NAME OF NINTH JOINT INVENTOR, IF ANY

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DATE

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